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EVALUATION OF RED CELL DISTRIBUTION WIDTH AND ITS CORRELATION WITH LEFT VENTRICULAR EJECTION FRACTION IN HEART FAILURE PATIENTS

Hardip Singh[1], Mayank Nausran[2], Permeet Kaur Bagga[3], Sameeksha Rathi[4], Rakesh Arora[5]

1. Professor, Department of Medicine, Government Medical College, Amritsar.
2. Junior Resident, Department of Medicine, Government Medical College, Amritsar.
3. Professor, Department of Pathology, Government Medical College, Amritsar
4. Junior Resident, Department of Psychiatry, Subharti Medical College, Meerut
5. Assistant Professor, Department of Endocrinology, Government Medical College, Amritsar

Corresponding Author

Dr. Rakesh Arora

Assistant Professor, Department of Endocrinology,

Government Medical College, Amritsar

Email ID: rakeshdec83@gmail.com

Contact no +91-9674011851

ABSTRACT

Background: Red cell distribution width (RDW) is a coefficient of variation of the distribution of individual red blood cell (RBC) volume, as determined by an automated blood cell counting instrument. Numerous studies conducted elsewhere have demonstrated increased RDW to be a significant prognostic marker in patients with heart failure (HF), both with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).

Aim: To study the relationship between RDW and left ventricular ejection fraction (LVEF), the most significant echocardiographic parameter of left ventricular systolic function, in patients with HF.

Methods: This study was a cross-sectional study conducted in 52 patients with HF who attended medical emergency/outpatient services of Guru Nanak Dev Hospital, Amritsar. In patients with HF, RDW was evaluated using an automated analyzer, while LVEF was determined by echocardiography. The correlation between RDW and LVEF was analyzed using the Pearson Correlation method.

Results: The Pearson Correlation coefficient between LVEF and RDW-CV was found to be -0.861, indicating a strong negative correlation. This correlation was statistically highly significant ($p < 0.001$) and remained significant even after adjusting for other potential confounding factors such as diabetes mellitus (DM), dyslipidemia, and hypertension (HTN).

Conclusion: RDW levels were higher in HF patients with low LVEF, correlating with left ventricular systolic dysfunction severity.

Keywords: Heart failure, RDW, LVEF

INTRODUCTION

HF is defined as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.[1] It can also be defined as a pathophysiological state in which an abnormality in cardiac function (structural or functional) leads to the heart's inability to pump blood at a rate required to meet the body's metabolic

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demands. When it does manage to do so, it occurs at high cardiac filling pressures.[2] Red cell distribution width (RDW) is a quantitative measure or numerical expression of anisocytosis. It is a coefficient of variation of the distribution of individual RBC volume, as determined by an automated blood cell counting instrument. High RDW value mirrors a large range in red cell size. It can be measured as either RDW- coefficient of variation (RDW-CV) or RDW-standard deviation (RDW-SD). RDW-CV is calculated from the formula (standard deviation of RBC volume/mean corpuscular volume) *100. It varies normally from 11.5 –14.5%. RDW-SD is regarded as the width of the distribution curve calculated arithmetically, measured at the 20% frequency level. It is a direct measure of calculating RDW.

RDW can increase in a variety of conditions, including inflammation, aging, oxidative stress, nutritional deficiencies and renal insufficiency. Numerous studies have demonstrated the association of elevated RDW with HF and poor echocardiographic markers. It has been shown to be a poor prognostic marker, associated independently with increased rates of cardiovascular and all-cause mortality, hospitalization for acute decompensation or worsened left ventricular function, length of hospital stay in patients with acute and chronic HF (HF). It is also a significant and independent predictor of developing HF in patients who currently do not have any signs or symptoms of HF.

This study was designed to assess the relationship between RDW and LVEF, the most significant echocardiographic parameter of left ventricular systolic function, in patients with HFpEF and HFrEF presenting at a tertiary care center in North India.

METHODS

Study design and setting:

This study was a cross-sectional study conducted in patients with HF (already diagnosed and newly diagnosed), who attended the medical emergency or outdoor department of Guru Nanak Dev Hospital, Amritsar, a tertiary care center in North India. This study was conducted in accordance with ethical principles that are consistent with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board/Ethics Committee. Written informed consent was obtained from all the patients prior to study commencement.

Inclusion and exclusion criteria:

The patients, either newly diagnosed or already diagnosed cases of HF (HFrEF and HFpEF), who were 18 years and above, were included in the study. Patients who refused to give consent, had liver disease, renal disease, or anemia with Hb of <12 g/dl, and those with a history of blood transfusion within the past 3 months or hematological malignancy were excluded from the study.

Data collection:

All eligible patients were subjected to a detailed history taking and clinical examination, including assessment of signs and symptoms of HF, the New York Heart Association (NYHA) classification of HF, risk factors such as smoking (smoking index >100), alcoholism (>14 units/week), hypertension, diabetes, dyslipidemia, coronary artery disease, and current and past medications. Biochemical investigations, including HbA1c, fasting and post-prandial plasma glucose, oral glucose tolerance test (if required), liver function tests, fasting lipid

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profile, and renal function tests were performed on all patients. A complete hemogram was performed in an automated cell counter Erba Mannheim H360. Hemoglobin, MCV, Hematocrit, RDW-CV and RDW-SD, amongst other parameters, were determined. Only RDW-CV values were used for statistical analysis. Normal range of RDW-CV was taken to be 11.5 to 14.5%. M-mode echocardiography was performed on these patients and echocardiographic parameters like LVEF, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV) were assessed.

Statistical analysis:

Statistical analysis was done with a statistical package of social sciences (SPSS) software ver. 26.0 and Epi Info 7.2.5.0. The difference of mean in RDW-CV in different NYHA classes was tested with ANOVA. The correlation between RDW-CV and LVEF was assessed with Pearson Correlation Coefficient. Linear regression analysis was done to evaluate the potential confounding effect of another variable that could have affected RDW-CV.

RESULTS

Table 1 depicts the baseline characteristics of the 52 patients enrolled for the study. The mean age of the patients included was 51.5 (15.47) years. Most of the patients were men (71.2%, n=37). Ischemic heart disease was the most common etiology of HF (59.6%, n=31). Most patients were in NYHA class 3 (65.4%, n=34) and the mean LVEF in these patients was 42 (12.9%). In the hematological markers, the mean hemoglobin was 13.5 (4.04) g/dL, the mean (SD) MCV was 89.6 (5.23) fL, and the mean RDW-CV value was 16.7 (2.78) %.

A statistically significant increase in RDW-CV values was observed as the NYHA class progressed from 2 to 4 (p-value < 0.001) (Table 2). On subgroup analysis, there was a significant increase in RDW-CV from NYHA class 2 to 3, 3 to 4 and 2 to 4 (results not shown). A highly significant negative correlation was found between RDW-CV and LVEF (r = -0.861, p-value < 0.001) (Fig. 1).

On analysis of correlations of various other variables that could potentially affect RDW-CV, we found that the presence of diabetes mellitus and dyslipidemia significantly increased RDW-CV (p values <0.001 and 0.002, respectively). Additionally, the presence of hypertension also increased RDW-CV but marginally failed to achieve the level of statistical significance (p=0.055). No statistically significant correlation was found between RDW-CV and age, gender, smoking, alcohol consumption, and the patient's Hb levels. Therefore, a multiple linear regression analysis was conducted with RDW-CV as the outcome variable and LVEF, DM, dyslipidemia, and HTN as independent variables (Table 3). On conducting multiple linear regression analysis, LVEF had a strong negative correlation with RDW-CV, even after adjusting for other variables that affected RDW-CV in single linear regression analyses. In fact, the effect of DM, dyslipidemia and HTN became non-significant in this model, with a much greater than 10% change from individual correlation coefficients, suggesting that the effect of these variables on RDW-CV is due to LVEF itself.

DISCUSSION

In this study, patients above 18 years of age were included. The youngest patient enrolled in the study was 20 years of age and the eldest one was 78 years of age. The majority of

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participants belonged to the age group of 40-49 and 60-69 years, each comprising 23.1%. Additionally, 19.2% of the individuals were in the age group between 50-59 years. This age group is most prone to risk factors of HF like HTN/ DM/ myocardial ischemia. Therefore, this can be why most of the patients admitted were of this age group. These values were further validated in a study by Van Craenenbrock EM[3], where most of the patients were of age 50-70 years and a study by Bozorgi et al. [4], where most patients were of age between 50-75 years.

In the present study, men accounted for 71.2% of the total, which was more than double the number of women, who constituted 28.8%. This may be due to males being more prone to cardiovascular diseases than females. Also, intake of alcohol and smoking is more common in males than females. The above values are positively correlated with that in study by Bozorgi A et al[4], where 74.3% were men and with that in Kawasoe S et al[5], where 69% were men.

The current study reports that most of the patients presented in the hospital were of NYHA class 3 (65.4%), followed by NYHA class 4, which constituted 19.4%. In a study by OH J et al[6], NYHA 3 plus 4 combined constitutes 83%. This could be because of the fact that it is a tertiary care center and most of the patients are present in the late stages of the disease.

These patients had a mean RDW-CV value of 16.7, which is well above the higher normal limit. The mean left ventricular ejection fraction in these patients was 42%, indicating that even patients with HFpEF were in significant proportion. In a study by Ferreira JP et al. [7], mean (SD) RDW-CV values were 15.4 (2.7) and ejection fraction values between 43.8 (11.1). Results of this study reveal a statistically highly significant negative correlation between left ventricular ejection fraction and RDW-CV. Furthermore, this correlation becomes stronger as the patients progress from NYHA class 2 to 4 of HF. The negative correlation between RDW-CV and left ventricular ejection fraction (LVEF) remained highly significant even after adjusting for other potential confounding factors, such as DM, dyslipidemia, and HTN. Interestingly, the effects of these conditions, as observed in individual analyses, were attenuated and became non-significant after adjusting for LVEF. This underscores the significance of LVEF as a key determinant in the association between RDW-CV and these confounding factors. The study's findings emphasize the importance of considering LVEF as a crucial factor when exploring the relationship between RDW-CV and clinical outcomes in patients with HF. This suggests that LVEF affects RDW-CV, independent of other potential confounding factors. RDW is a useful prognostic marker not only for HF but also for atherosclerotic diseases, such as coronary artery disease or carotid artery disease[5]. In a study conducted by Bozorgi A et al[4] , pearson correlation analysis demonstrated a significant ($p<0.001$) but weak negative correlation ($r=-0.268$) between RDW and LVEF. In a study by Senthong V et al. [8], high RDW values were significantly associated ($p = 0.04$) with LVEF < 40% in patients with HF. In a study by Ferreira J Petal[7], RDW is associated with LVEF having $p <0.05$, which is highly significant.

LIMITATION

The study had limitations of small sample size and single-center setting, requiring validation through larger, multi-institutional studies. Secondly, this is a cross-sectional study. A clear association of increased RDW with poor prognosis in patients with HF can be established by long-term prospective survival studies. Furthermore, it is important to note that 83% of the patients

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enrolled in the study had NYHA class 3 or 4 HF. As a result, the findings of this study may be more applicable to patients with severe HF and may not be as relevant to those with lesser severity of the condition.

CONCLUSION

RDW levels are increased amongst patients with HF patients with low LVEF have elevated RDW levels compared with normal left ventricular ejection fraction. Additionally, the association was independent of the presence of other potential confounding factors. Therefore, in conclusion, RDW correlates with the severity of left ventricular systolic dysfunction. Thus, it can be used as a simple parameter that can help in assessing the severity of HF. This finding becomes particularly relevant in settings with poor resources where access to echocardiography may not be readily available.

CONFLICTS OF INTEREST: None

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Tables

Table 1: Baseline Characteristics of the patients enrolled for the study

Characteristics	**Number of patients (N=52)**
Age, years, mean (SD)	51.5 (15.47)
Sex	
Males	37 (71.2)
Females	15 (28.8)
Risk Factors for HF	
Diabetes Mellitus	19 (36.5)
Hypertension	21 (40.4)
Dyslipidemia	17 (32.7)
Smoking	9 (17.3)
Significant Alcohol intake	22 (42.3)
Prior CAD	10 (19.2)
Prior hospitalization for HF	11 (21.1)
Underlying Etiology of HF	
Ischemic heart disease	31 (59.6)
Rheumatic heart disease	5 (9.5)
Calcific AS/AR	2 (3.9)
Alcoholic Cardiomyopathy	2 (3.9)
DCM – unknown cause	3 (5.8)
Peripartum Cardiomyopathy	1 (1.9)
Right Ventricular Dysfunction	2 (3.9)
CHD with Eisenmenger's Complex	1 (1.9)
Myocarditis	1 (1.9)
Cor pulmonale	4 (7.7)
NYHA Class	
Class 1	0
Class 2	8 (15.4)
Class 3	34 (65.4)
Class 4	10 (19.2)
LVEF, %, mean (SD)	42 (12.9)
RDW-CV, %, mean (SD)	16.7 (2.78)
Hemoglobin, g/dL, mean (SD)	13.5 (4.04)
MCV, fL, mean (SD)	89.6 (5.23)

Data shown as n (%).

AR, aortic regurgitation; AS, aortic stenosis; CAD, coronary artery disease, CHD, congenital heart disease; DCM, dilated cardiomyopathy, HF, heart failure; LVEF, left ventricular ejection fraction, MCV, mean corpuscular volume, NYHA – New York Heart Association, RDW-CV – Red Cell Distribution Width - Coefficient of Variation, SD – Standard Deviation.

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Table 2: Comparison of RDW-CV according to NYHA Functional Class

NYHA Functional Class	RDW-CV	p-value
1	-	<0.001
2	13.30 (0.66)	
3	16.40 (2.02)	
4	20.40 (1.67)	

Data represented as mean (SD).
NYHA, New York heart association, RDW-CV, red cell distribution width-coefficient of variation

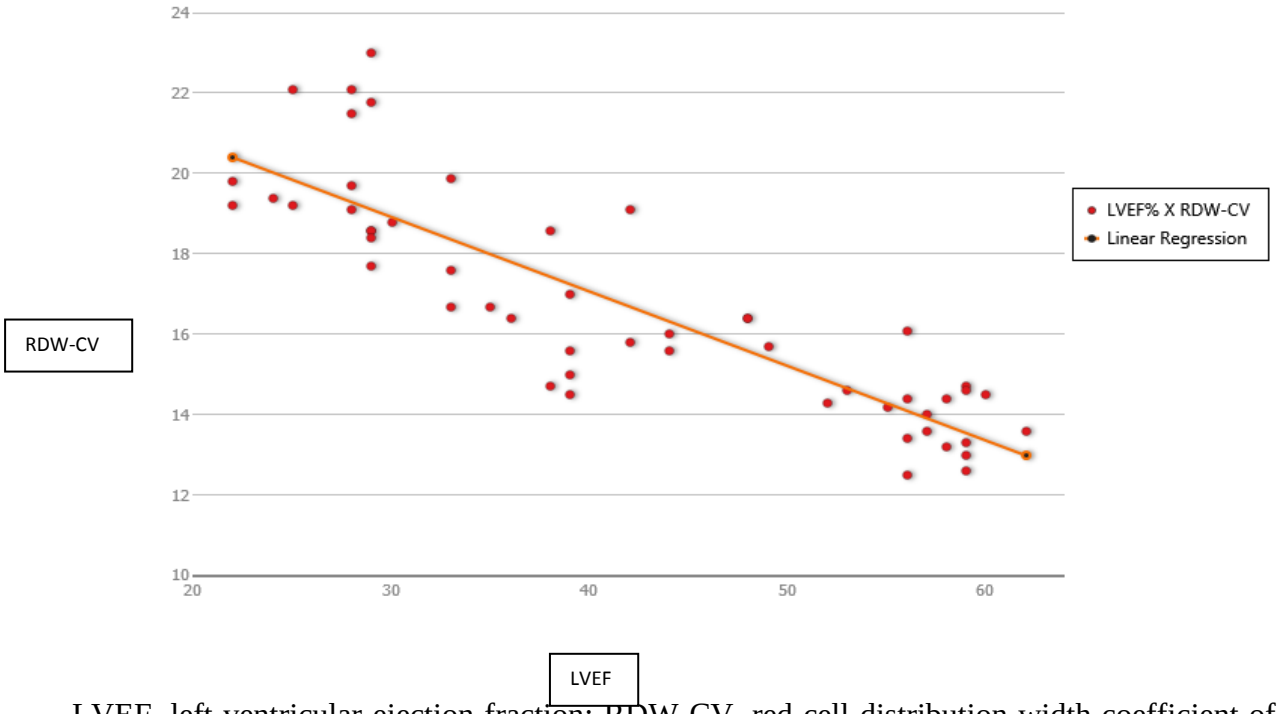
Table 3: Multiple linear regression analysis for potential confounding factors

Variable	Regression Coefficient	P-value
DM	0.665	0.144
Dyslipidemia	0.481	0.328
HTN	0.305	0.491
LVEF (%)	-0.166	<0.001

DM, diabetes mellitus; HTN, hypertension; LVEF, left ventricular ejection fraction; RDW-CV, red cell distribution width-coefficient of variation.

Figure legend

Figure 1: Scatter Diagram depicting association of LVEF with RDW-CV



LVEF, left ventricular ejection fraction; RDW-CV, red cell distribution width-coefficient of variation